The Current Status of Ongoing Clinical Trials: Beyond 3 Hours

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Overview

Randomized acute ischemic stroke trials have shown no clear benefit for intravenous tPA when given beyond the currently approved 3 hour time cut-off. This is a serious practical limitation, since only about 1/5 of patients arrive in time to be eligible for treatment. However, these trials were based on simple CT selection criteria only. More recent reperfusion trial designs have successfully incorporated perfusion-diffusion MRI mismatch into triage and selection criteria. Data from the desmoteplase trials show the potential to push the IV treatment window out to 9 hours or more, with excellent recanalization, low hemorrhage rates, and improved patient outcomes. Late thrombolysis selection paradigms are moving from the 'ticking clock' to the 'tissue clock [1].'

Current status and trends in thrombolysis

Tissue plasminogen activator (tPA) has been approved for acute ischemic stroke treatment for 10 years(Hacke, 1995 and 1998). This was an important first step in stroke treatment, and remains the only FDA-approved drug today. Kleindorfer has shown that only 22% of stroke victims arrive within the 3 hour time cut-off, and 51% of these have other contraindications to tPA (Kleindorfer 2004). Treatment based on CT selection criteria has shown rapidly diminishing benefits beyond 3 hours, crossing over to parity after about 4.5 hours in group statistics[2]. The prohibitively short time window and fear of post-thrombolytic bleeding have limited widespread adoption of tPA: only about 4% of strokes receive tPA in the United States today. This means that 96% of patients are either offered no treatment or must be managed off-label.

MRI-based perfusion and diffusion now offer the opportunity to rapidly screen patients to help select those who might be good candidates for revascularization, even beyond 3 hours. Perfusion is central to understanding the functional status of collateral flow and autoregulation, which are key issues in determining tissue viability in the first hours after stroke onset [3]. Individual treatment decisions can then be based on individual data, not an arbitrary time cut-off point based on group data. Several stroke trials in progress or nearing completion have used time windows with treatment guided by advanced imaging both to select patients and to assess intended effects of intervention (Table 1).

The goal of acute stroke imaging is several-fold. The protocol must reliably confirm stroke as the correct diagnosis and exclude stroke mimics such as tumor or infection. The approach must accurately detect hemorrhage and distinguish bland from hemorrhagic infarction. For optimal selection of thrombolysis candidates, the protocol should include all those likely to benefit, while simultaneously excluding those who would have unacceptable risk. Many stroke experts agree the

best target population may be those with a penumbral 'tissue at risk' pattern identified on perfusion images. According to this construct, a large perfusion defect, indicative of oligemic tissue at risk, with a smaller area of ischemic injury on diffusion, indicates penumbral tissue that may be a good candidate for urgent revascularization. CT perfusion parameters can also provide similar physiologic information to help guide therapy. The penumbral pattern is seen in a majority of stroke patients imaged within several hours of stroke onset, supporting the notion that imaging-based selection could improve outcomes in thrombolysis through improved patient selection[4-6].

PROACT II is the only randomized, placebo controlled thrombolysis trial to show benefit in acute ischemic stroke at the 3-6 hour time window. In this trial, selection was based on CT (similar to tPA criteria) but also required angiographic proof of MCA occlusion. Even with a 6 hour window, excellent recanalization rates (66% vs 18% control), positive clinical outcomes (40% vs 25% control), and acceptable symptomatic intracranial hemorrhage rates were observed (10% vs 2% control) in PROACT II. Although the drug was not approved by the FDA, this trial showed the potential to successfully treat stroke patients at timepoints beyond 3 hours using advanced imaging selection coupled with effective thrombolysis.

The recently published DIAS trial and presentation of DEDAS results show the treatment window can be successfully stretched to 3-9 hours using a novel IV thrombolytic drug and MRI-based selection [1, 7]. Desmoteplase was originally isolated from the common South American vampire bat, *Desmodus rotundus* (but is thankfully now made through recombinant techniques). Desmoteplase is a highly fibrin specific plasminogen activator, is not activated by beta amyloid, and has a long half life (~4-5 hours), all of which are favorable pharmacologic features for use in acute stroke. DIAS and DEDAS used essentially identical MRI-based perfusion-diffusion mismatch protocols for selection.. A mismatch was defined as a perfusion defect visually 20% larger in diameter than the diffusion defect in the same slice. The perfusion abnormality had to be at least 2 cm in diameter, involve cortex, and had to be obvious. To ensure sensitivity, perfusion was based on dynamic MTT or TTP maps, or even simple review of the raw the EPI T2* dynamic images. Reperfusion was judged by the presence of MRA recanalization (TIMI improvement by 2 points) or perfusion parameter improvement (MTT volume reduction by at least 30%). High reperfusion rates (46.7-71.4% vs 19.2% control) were seen. Although these were small trials, positive clinical outcomes were also seen (46.7-60% vs 22.2% control), and low symptomatic bleeding rates (~1%) were found for the weight-adjusted dose tiers at 90 and 125 μg/kg levels in DIAS. In unpublished data, it has also been reported that baseline diffusion lesion size partially reversed on follow-up in the 125 μg/kg group [8]. Based on these promising results, the DIAS-2 trial has now begun recruitment.

Patient-related risk factors in thrombolysis

Large randomized trials have shown that older age, more severe baseline stroke deficits (high NIH stroke scale scores), and elevated serum glucose levels have all been found to confer poor outcome or higher risk when thrombolysis is undertaken. More controversial are the imaging features and findings that might be best used to exclude or include individual patients. These will undoubtedly be the focus of ongoing research for the next several years.

Hot topic: Should Microbleeds be an Exclusion for Thrombolysis?

Amyloid-related cerebral microhemorrhages, or microbleeds, have been anecdotally linked to post-thrombolytic brain hemorrhage in a handful of cases. These lesions are characterized by amyloid deposition in small arteries, detected as focal dots or blotches of hemosiderin on MR images. Microbleeds are therefore best seen on gradient echo recalled T2* or susceptibility-

weighted MR [9] and at higher field strengths. Amyloid is a disease of the elderly, with incidence and multiplicity of lesions rising sharply after age 60. This small vessel vasculopathy of unknown origin has been linked to recurrent ischemic stroke, lobar hemorrhage, and advanced white matter disease [10-12]. CT cannot detect amyloid-related microbleeds, so these were never visible or considered in the large tPA trials. However, more widespread use of MR for stroke triage has made it inevitable that such lesions will be encountered during stroke work-ups, and we must now decide what to do with this observation. Despite scattered reports of bleeding into amyloid, the risk of post thrombolytic hemorrhage is likely to be low (? <1%) based on data from large myocardial thrombolysis trials [13]. Whether microhemorrhages should be taken into account in excluding patients from thrombolysis is unknown. Since we know benefit was still seen for tPA despite the inevitable inclusion of amyloid cases, our approach is not to exclude based on presence of microbleeds. Clearly more work needs to be done to establish guidelines – we need to know if we should specifically look with T2* in stroke triage, and what to do if microbleeds are observed.

Low ADC values predict hemorrhagic transformation post lysis

Large lesions with severely decreased ADC values generally predict poor outcome and also greater likelihood of post-thrombolysis hemorrhage [14-17]. Visual qualitative assessment of DWI and ADC images works as well as quantitative pixel-based analysis, likely due to DWI heterogeneity within the lesion [18]. It must be noted however that hemorrhagic transformation is very common after infarction, and that hemorrhage occurring within a reperfused territory may not necessarily be bad per se [19, 20]. The type of hemorrhagic transformation (petechial vs hematoma) and ultimately, whether it is accompanied by symptomatic neurologic decline are the critical determinants in real-world patient outcome.

Perfusion Thresholds and Patient Selection

Dynamic maps (MTT or TTP) are the most sensitive for detection of tissue being abnormally perfused. However, these should be viewed as 'worst case scenario' since they tend to overestimate tissue at risk of actual infarction since some portion may be well compensated [21]. Butcher and several other investigators have refined thresholds in an attempt to make these makes more specific to detection of impending infarction [22]. However, it can be argued that maximal sensitivity is a favorable feature when screening for abnormal blood delivery [23]. Since acute revascularization treatment explicitly sets forth to reverse the defect, a more specific threshold may not be required or even desirable for routine middle of the night management. In the only blinded trial data available, the simplest gross dynamic maps or even qualitative inspection of PWI image loops were successful for penumbral identification in the DIAS and DEDAS trials.

The CBV reflects autoregulatory status, and when severely depressed indicates morbidly ischemic core tissue likely to undergo infarction [24]. Low CBV can predict not only poor outcome for that tissue but also higher likelihood of hemorrhagic transformation if the tissue is reperfused [25]. Wintermark has shown a low CBV may provide the perfusion CT equivalent of diffusion in MR. His group has demonstrated very high correlations between low CBV on perfusion CT and DWI in acute stroke patients imaged acutely in back to back exams [26]. He has also proposed that CT perfusion parameters including a long MTT (>1.45 compared to opposite) and low CBV (<2 ml/100gm) may predict tissue destined to infarction (presented at ASNR, Toronto, 2005). Mismatches based on low cortical CBV (approximately less than normal white matter) and larger surrounding CBF or MTT defects may provide the practical CT correlate of PWI-DWI mismatch. Some of these issues have been reviewed recently by Wintermark [27].

The ability for any particular imaging parameter to predict risk depends on how the study evaluates outcome, whether hemorrhages are judged to be symptomatic or not, and the details of

treatment, including thrombolytic drugs. For practical purposes, MTT tends to overestimate tissue at risk, CBV tends to underestimate risk, and CBF is somewhere in between. Among conservatively managed patients (no thrombolytics) it has been generally observed that relative CBF values are good predictors of viability versus infarction [28-30]. Other groups have proposed using TTP prolongations of ~4-5 seconds, peak height less than 54% [31], and severe ADC decreases as predictors of lesion growth or malignant edema [32]. When perfusion parameters are being used in patients treated with thrombolytics, predictive models based on conservative treatments do not fully apply.

In recent work, specific perfusion parameters have been advanced as strong predictors of late infarct volume (TTP), irreversible core (Tmax), and lesion growth (low CBF) [33-35]. Butcher et al have recently reviewed the topic of perfusion thresholds based on their initial 40 patients in the EPITHET database [22]. A multicenter review regarding MR criteria for thrombolysis, including detailed protocols, is available from Hjort et al [36].

Blood-brain barrier Damage and Reperfusion Hemorrhage

The integrity of the ischemic blood-brain barrier (BBB) is probably crucial in controlling the risk of late thrombolysis. Cerebral microvessels undergo progressive ischemic injury in the minutes and hours after occlusion or reperfusion [37, 38]. These changes may contribute to no reflow phenomena, permeability increases, petechial hemorrhage, and leakage of proteins and gadolinium. Perfusion studies may also indicate loss of vasomotor tone and autoregulation, with 'luxury perfusion' patterns sometimes observed after delayed re-opening of vessels, as would be expected from animal data [39, 40].

Signs of pre-exiting parenchymal enhancement before treatment strongly predict subsequent hemorrhage after thrombolysis [41-44]This presumably reflects the notion that a leaky BBB is the manifestation of severe ischemic endothelial and tight junction damage, a set-up for reperfusion bleeding. Controlled data are not yet available to be able to say whether this should become an exclusion criterion for thrombolysis candidates, but available data suggest caution when this finding is observed

Kassner, Roberts and colleagues have recently reported MR-based permeability measurements in the triage of acute stroke patients [45]. Focal elevations of permeability were seen within the centers of the diffusion defects, and abnormal permeability changes were correlated with later hemorrhagic transformation. Roberts has suggested this may be 'the core of the core' – a profoundly injured bit of brain in the center of the diffusion lesion. Further studies will be needed to establish whether this metric should be integrated into stroke triage at later timeframes.

Table 1: Currently Active Stroke Trials Beyond 3 Hours*

Trial Acronym	Drug / Device	Time Range (hours)	Imaging Modality / Selection	Description / Comments
AbESTT - II	IV abciximab	< 5 and 5-6 arms	Standard	Halted Fall 2005 due to safety concerns
DEFUSE	IV tPA (no control arm)	3-6	MR PWI-DWI mismatch	Open label study; results expected Spring 2006
DIAS-2	IV desmoteplase	3-9	MR PWI-DWI or pCT mismatch	First randomized, placebo-controlled trial to use perfusion CT for selection.
EPITHET	IV tPA vs placebo	3-6	CT selection; PWI-DWI also obtained acutely	Treatment is given according to CT criteria, but MR data are also being collected. Will be key data re: mismatch hypothesis. As of May 2005, 72 of 100 recruited.
IMS II	IV then IA tPA, assisted by EKOS ultrasound device	3 for IV, followed by IA for 2 hrs	CT, then conventional angiography	
IST-3	IV tPA	3-6	CT or MR	Study begun in year 2000, with plan to recruit 6000 subjects. As of May 2005, only 352 enrolled.
MR Rescue	IA Concentric clot retriever	0-8	MR PWI-DWI mismatch	Early data show benefit for treatment when mismatch is present
ROSIE	IV abciximab and retaplase	3-24	One arm with CT, the other with MR PWI-DWI mismatch	Open label dose escalation design
SaTIS	IV Tirofiban + tPA	6-22	Standard	Placebo controlled, randomized

*****Primary source of information for this table comes from the Stroke Trials Directory website: http://www.strokecenter.org/trials, supplemented by recent meeting presentations and personal correspondence with several of the trialists. Modified from original tabulation performed by Rowley, HA, Neuroimaging Clinics of North America, in press, 2005.

AbESTT – II: Abciximab in Emergent Stroke Treatment Trial – II
DEFUSE: Diffusion-weighted imaging Evaluation For Understanding Stroke Evolution
DIAS-2: Desmoteplase in Acute Ischemic Stroke-2
EPITHET: Echoplanar Imaging Thrombolysis Evaluation Trial
IMS II: Interventional Management of Stroke Study
IST-3: Third International Stroke Trial
MR Rescue: MR and Recanalization of Stroke Clots Using Embolectomy
ROSIE: ReoPro Retavase Reperfusion of Stroke Safety Study -- Imaging Evaluation
SaTIS: Safety of Tirofiban in Acute Ischemic Stroke

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